

**Clinical trial results:**

A MULTI-CENTRE, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, TWO-ARMED, PARALLEL GROUP STUDY TO EVALUATE EFFICACY AND SAFETY OF INTRAVENOUS (IV) SILDENAFIL IN THE TREATMENT OF NEONATES WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN) OR HYPOXIC RESPIRATORY FAILURE (HRF) AND AT RISK FOR PPHN, WITH A LONG TERM FOLLOW-UP INVESTIGATION OF DEVELOPMENTAL PROGRESS 12 AND 24 MONTHS AFTER COMPLETION OF STUDY TREATMENT

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2012-002619-24 |
| Trial protocol | BE GB SE ES AT DE NO IT NL DK FR |
| Global end of trial date | 28 September 2020 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 08 April 2021 |
| First version publication date | 17 July 2019 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Basic Results being posted with final data / end of global study date need to be added to results |

Trial information**Trial identification**

| | |
|-----------------------|----------|
| Sponsor protocol code | A1481316 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01720524 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000671-PIP01-09 |

| | |
|--|-----|
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 January 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of IV sildenafil when added to inhaled nitric oxide (iNO) for the treatment of neonates with PPHN or HRF and at risk for PPHN.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

All subjects were treated with iNO.

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 05 August 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Canada: 3 |
| Country: Number of subjects enrolled | Denmark: 4 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Netherlands: 5 |
| Country: Number of subjects enrolled | Norway: 1 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | Sweden: 8 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | United States: 19 |

| | |
|------------------------------------|----|
| Worldwide total number of subjects | 59 |
| EEA total number of subjects | 27 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 59 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted in two parts Part A (double-blind phase) and Part B (long-term, non-interventional phase).

Pre-assignment

Screening details:

Neonates with PPHN or HRF and at risk of PPHN who were receiving iNO treatment were evaluated in this study.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Part A (Double-blind Phase) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Assessor, Carer, Subject, Monitor, Data analyst |

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | IV Sildenafil |

Arm description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sildenafil Citrate |
| Investigational medicinal product code | UK-092,480 |
| Other name | Revatio |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

IV sildenafil at a loading dose of 0.1 mg/kg, for 30 minutes, on Day 1, followed by maintenance dose of 0.03 mg/kg/hr, for a minimum of 2 days and maximum of 14 days.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|--|---------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo (0.9 percent [%] normal saline or dextrose 10%) intravenously for a minimum of 2 days and maximum of 14 days.

| Number of subjects in period 1 | IV Sildenafil | Placebo |
|---------------------------------------|---------------|---------|
| Started | 29 | 30 |
| Completed | 22 | 18 |
| Not completed | 7 | 12 |
| Consent withdrawn by subject | - | 1 |
| Missed 28 day follow-up visit | 1 | 1 |
| Other | - | 1 |
| Adverse event | 2 | 2 |
| Insufficient Clinical Response | 2 | 4 |
| Death (during follow-up) | - | 1 |
| Death (not completed study treatment) | 2 | - |
| Lost to follow-up | - | 1 |
| Protocol deviation | - | 1 |

Period 2

| | |
|------------------------------|-----------------------------------|
| Period 2 title | Part B (Non-Interventional Phase) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | IV Sildenafil |

Arm description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Placebo |

Arm description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2 | IV Sildenafil | Placebo |
|---|---------------|---------|
| Started | 22 | 18 |
| Completed | 22 | 17 |
| Not completed | 5 | 9 |
| Death | - | 2 |
| No longer willing to participate in study | 1 | 4 |
| Unspecified | 2 | - |
| Lost to follow-up | 2 | 3 |
| Joined | 5 | 8 |
| Continued to follow-up | 5 | 8 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | IV Sildenafil |
|-----------------------|---------------|

Reporting group description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| Reporting group values | IV Sildenafil | Placebo | Total |
|---|---------------|---------|-------|
| Number of subjects | 29 | 30 | 59 |
| Age Categorical | | | |
| Safety population included all subjects treated with study treatment. | | | |
| Units: Subjects | | | |
| Newborns (0-27 days) | 29 | 30 | 59 |
| Age Continuous | | | |
| Safety population included all subjects treated with study treatment. | | | |
| Units: days | | | |
| arithmetic mean | 1.7 | 1.9 | |
| standard deviation | ± 0.90 | ± 0.75 | - |
| Gender Categorical | | | |
| Safety population included all subjects treated with study treatment. | | | |
| Units: Subjects | | | |
| Female | 13 | 13 | 26 |
| Male | 16 | 17 | 33 |
| Race | | | |
| Safety population included all subjects treated with study treatment. | | | |
| Units: Subjects | | | |
| White | 19 | 16 | 35 |
| Black | 1 | 7 | 8 |
| Asian | 2 | 5 | 7 |
| Other | 3 | 1 | 4 |
| Unspecified | 4 | 1 | 5 |

End points

End points reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | IV Sildenafil |
|-----------------------|---------------|

Reporting group description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|-----------------------|---------------|
| Reporting group title | IV Sildenafil |
|-----------------------|---------------|

Reporting group description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|----------------------------|--|
| Subject analysis set title | Part B (Non-Interventional Phase): IV Sildenafil |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|----------------------------|--|
| Subject analysis set title | Part B (Non-Interventional Phase): Placebo |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Primary: Time on Inhaled Nitric Oxide (iNO) Treatment After Initiation of Intravenous (IV) Study Drug For Subjects Without Treatment Failure

| | |
|-----------------|---|
| End point title | Time on Inhaled Nitric Oxide (iNO) Treatment After Initiation of Intravenous (IV) Study Drug For Subjects Without Treatment Failure |
|-----------------|---|

End point description:

Time in days, on iNO treatment, for subjects without iNO treatment failure, was calculated 14 days from the initiation of IV study drug or hospital discharge, whichever occurred first. iNO treatment failure was defined as need for additional treatment targeting PPHN, need for extra corporeal membrane oxygenation (ECMO), or death during the study. The intent-to-treat population (ITT) included all randomized subjects treated with study treatment. Here, "Number of Subjects Analyzed" signifies number of subjects without iNO treatment failure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

14 days from the initiation of IV study drug or hospital discharge, whichever occurs first

| End point values | IV Sildenafil | Placebo | | |
|--|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 24 | | |
| Units: days | | | | |
| least squares mean (confidence interval 95%) | 4.1 (2.58 to 5.58) | 4.1 (2.70 to 5.50) | | |

Statistical analyses

| Statistical analysis title | IV Sildenafil vs. Placebo |
|--|-----------------------------------|
| Statistical analysis description: | |
| Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database (sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis. | |
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.985 |
| Method | ANCOVA |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.08 |
| upper limit | 2.04 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.02 |

Primary: Treatment Failure Rate

| End point title | Treatment Failure Rate |
|---|------------------------|
| End point description: | |
| Treatment failure rate was defined as percentage of subjects who needed additional treatment targeting PPHN, needed ECMO, or died during the study. The ITT population included all randomized subjects treated with study treatment. | |
| End point type | Primary |
| End point timeframe: | |
| 14 days from the initiation of IV study drug or hospital discharge, whichever occurs first | |

| End point values | IV Sildenafil | Placebo | | |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 27.6 (11.3 to 43.9) | 20.0 (5.7 to 34.3) | | |

Statistical analyses

| Statistical analysis title | IV Sildenafil vs. Placebo |
|---|---------------------------|
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4935 |
| Method | Chi-squared |
| Parameter estimate | Difference in percentage |
| Point estimate | 7.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.1 |
| upper limit | 29.3 |

Secondary: Time From Initiation of Intravenous (IV) Study Drug to Final Weaning of Mechanical Ventilation

| | |
|--|--|
| End point title | Time From Initiation of Intravenous (IV) Study Drug to Final Weaning of Mechanical Ventilation |
| End point description: | |
| Time in days, from initiation of IV study drug to final weaning of mechanical ventilation among subjects achieving final weaning of mechanical ventilation for PPHN was evaluated. Kaplan-Meier method was used for estimation. For subjects with mechanical ventilation beyond 336 hours (14 days) from initiation of IV study drug, data is censored at 14 days. The ITT population included all randomized subjects treated with study treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| 14 days from the initiation of IV study drug or hospital discharge, whichever occurs first | |

| End point values | IV Sildenafil | Placebo | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 8.3 (5.46 to 11.75) | 7.3 (5.46 to 10.78) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | IV Sildenafil vs. Placebo |
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9885 |
| Method | Logrank |

Secondary: Time From Initiation of Intravenous (IV) Study Drug to First Treatment Failure

| | |
|-----------------|--|
| End point title | Time From Initiation of Intravenous (IV) Study Drug to First Treatment Failure |
|-----------------|--|

End point description:

Time in days, from initiation of IV study drug to first treatment failure (defined as need for additional treatment targeting PPHN, need for ECMO, or death) for subjects with treatment failure was evaluated. Kaplan-Meier method was used for estimation. For subjects without treatment failure by the endpoint assessment date, data is censored at the endpoint assessment date. The ITT population included all randomized subjects treated with study treatment. Due to low number of subjects with events, Kaplan-Meier estimates of median, upper and lower limit of CI could not be estimated/calculated and has been denoted by "99999", signifying data not available.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

14 days from the initiation of IV study drug or hospital discharge, whichever occurs first

| | | | | |
|----------------------------------|-------------------------|-------------------------|--|--|
| End point values | IV Sildenafil | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | | |

Statistical analyses

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | IV Sildenafil vs. Placebo |
| Comparison groups | IV Sildenafil v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.491 |
| Method | Logrank |

Secondary: Percentage of Subjects With Individual Components of Treatment Failure

| | |
|---|--|
| End point title | Percentage of Subjects With Individual Components of Treatment Failure |
| End point description: Percentage of subjects with individual components of treatment failure (need to start additional treatment targeting PPHN, need to start ECMO, or death) were evaluated. Some subjects could have had multiple qualifying events for treatment failure. The ITT population included all randomized subjects treated with study treatment. | |
| End point type | Secondary |
| End point timeframe: 14 days from the initiation of IV study drug or hospital discharge, whichever occurs first | |

| End point values | IV Sildenafil | Placebo | | |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Additional Treatment Targeting PPHN | 13.8 (3.9 to 31.7) | 10.0 (2.1 to 26.5) | | |
| ECMO | 10.3 (2.2 to 27.4) | 10.0 (2.1 to 26.5) | | |
| Death | 6.9 (0.8 to 22.8) | 0.0 (0.0 to 11.6) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | IV Sildenafil vs. Placebo: Additional Treatment |
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7065 |
| Method | Fisher exact |
| Parameter estimate | Difference in Percentage |
| Point estimate | 3.8 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.2 |
| upper limit | 22.9 |

| | |
|---|---------------------------------|
| Statistical analysis title | IV Sildenafil vs. Placebo: ECMO |
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.999 |
| Method | Fisher exact |
| Parameter estimate | Difference in Percentage |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.5 |
| upper limit | 18.5 |

| | |
|---|----------------------------------|
| Statistical analysis title | IV Sildenafil vs. Placebo: Death |
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2373 |
| Method | Fisher exact |
| Parameter estimate | Difference in Percentage |
| Point estimate | 6.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.5 |
| upper limit | 22.8 |

Secondary: Change From Baseline in Oxygenation Index (OI) at Hour 6, 12 and 24

| | |
|-----------------|---|
| End point title | Change From Baseline in Oxygenation Index (OI) at Hour 6, 12 and 24 |
|-----------------|---|

End point description:

Oxygenation index was calculated as the product of fraction of inspired oxygen (FiO2) and mean airway pressure divided by partial pressure of oxygen dissolved in arterial blood (PaO2) [(FiO2*mean airway pressure)/PaO2] measured in centimeter of water per millimeter of mercury (cmH2O/mmHg). FiO2 is the measure of oxygen concentration that is breathed. Mean airway pressure is defined as an average of the airway pressure throughout the respiratory cycle. PaO2 is the measure of oxygen level dissolved in

the arterial blood. Here, 'n' = subjects evaluable for this endpoint at specified time points. The ITT population included all randomized subjects treated with study treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Hour 6, 12 and 24 after start of infusion

| End point values | IV Sildenafil | Placebo | | |
|--|-------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: cmH2O/mmHg | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Change at Hour 6 (n=29,22) | -4.2 (-11.64 to 3.34) | -8.0 (-16.63 to 0.57) | | |
| Change at Hour 12 (n=28,22) | -4.1 (-10.51 to 2.23) | -8.2 (-15.42 to -1.04) | | |
| Change at Hour 24 (n=18,17) | -11.6 (-15.40 to -7.83) | -9.5 (-13.36 to -5.57) | | |

Statistical analyses

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|-----------------------------------|-----------------------------------|
| Statistical analysis title | IV Sildenafil vs. Placebo: Hour 6 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database

(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

| | |
|---|-------------------------|
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4984 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 3.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.5 |
| upper limit | 15.3 |

| | |
|-----------------------------------|------------------------------------|
| Statistical analysis title | IV Sildenafil vs. Placebo: Hour 12 |
|-----------------------------------|------------------------------------|

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database

(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which

may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

| | |
|---|-------------------------|
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3956 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 4.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.5 |
| upper limit | 13.7 |

| | |
|--|------------------------------------|
| Statistical analysis title | IV Sildenafil vs. Placebo: Hour 24 |
| Statistical analysis description: | |
| Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database (sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis. | |
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4249 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.6 |
| upper limit | 3.3 |

Secondary: Change From Baseline in Differential Saturation at Hour 6, 12 and 24

| | |
|---|--|
| End point title | Change From Baseline in Differential Saturation at Hour 6, 12 and 24 |
| End point description: | |
| Differential oxygenation saturation is a simple way to detect the right-to-left shunting at ductus arteriosus using 2 pulse oximeters. It is the difference between pre-ductal and post-ductal sites pulse oxygen saturation (SpO2). Where, pre-duct refers to right upper extremity and post-duct refers to lower limb. Oxygenation saturation is measured as percentage of hemoglobin binding sites occupied by oxygen in the blood. Here, 'n' = subjects evaluable for this endpoint at specified time points. The ITT population included all randomized subjects treated with study treatment. | |
| End point type | Secondary |

End point timeframe:

Baseline, Hour 6, 12 and 24 after start of infusion

| End point values | IV Sildenafil | Placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: percentage of hemoglobin | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Change at Hour 6 (n=26,19) | 1.5 (-1.79 to 4.80) | 0.8 (-3.10 to 4.62) | | |
| Change at Hour 12 (n=25,19) | -1.2 (-7.65 to 5.21) | 6.7 (-0.65 to 14.12) | | |
| Change at Hour 24 (n=19,14) | 1.2 (-7.15 to 9.49) | 9.3 (-0.40 to 19.08) | | |

Statistical analyses

| Statistical analysis title | IV Sildenafil vs. Placebo: Hour 6 |
|----------------------------|-----------------------------------|
|----------------------------|-----------------------------------|

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database

(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

| | |
|---|-------------------------|
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7686 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.3 |
| upper limit | 5.8 |

| Statistical analysis title | IV Sildenafil vs. Placebo: Hour 12 |
|----------------------------|------------------------------------|
|----------------------------|------------------------------------|

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database

(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

| | |
|-------------------|-------------------------|
| Comparison groups | IV Sildenafil v Placebo |
|-------------------|-------------------------|

| | |
|---|--------------------|
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1112 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.8 |
| upper limit | 1.9 |

| | |
|-----------------------------------|------------------------------------|
| Statistical analysis title | IV Sildenafil vs. Placebo: Hour 24 |
|-----------------------------------|------------------------------------|

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database

(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

| | |
|---|-------------------------|
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2089 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -8.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.2 |
| upper limit | 4.8 |

Secondary: Change From Baseline in Ratio of Partial Pressure of Oxygen in Arterial Blood to Fraction of Inspired Oxygen (P/F) at Hour 6, 12 and 24

| | |
|-----------------|---|
| End point title | Change From Baseline in Ratio of Partial Pressure of Oxygen in Arterial Blood to Fraction of Inspired Oxygen (P/F) at Hour 6, 12 and 24 |
|-----------------|---|

End point description:

The ratio of partial pressure of arterial oxygen to fraction of inspired oxygen is a ratio between the oxygen level in the arterial blood and the oxygen concentration that is breathed. It helps to determine the degree of any problems with how the lungs transfer oxygen to the blood. Here, 'n' = subjects evaluable for this endpoint at specified time points. The ITT population consisted of all randomized subjects treated with study treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Hour 6, 12 and 24 after start of infusion

| End point values | IV Sildenafil | Placebo | | |
|--|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: ratio | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Change at Hour 6 (n=29,23) | 45.3 (17.21 to 73.37) | 8.1 (-23.48 to 39.60) | | |
| Change at Hour 12 (n=28,24) | 43.4 (16.76 to 70.13) | 16.9 (-11.97 to 45.68) | | |
| Change at Hour 24 (n=20,17) | 94.6 (18.52 to 170.69) | 14.7 (-67.83 to 97.25) | | |

Statistical analyses

| Statistical analysis title | IV Sildenafil vs. Placebo: Hour 6 |
|--|-----------------------------------|
| Statistical analysis description: | |
| Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database (sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis. | |
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0829 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 37.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5 |
| upper limit | 79.5 |

| Statistical analysis title | IV Sildenafil vs. Placebo: Hour 12 |
|--|------------------------------------|
| Statistical analysis description: | |
| Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database (sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis. | |
| Comparison groups | IV Sildenafil v Placebo |

| | |
|---|--------------------|
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1802 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 26.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.7 |
| upper limit | 65.9 |

| | |
|-----------------------------------|------------------------------------|
| Statistical analysis title | IV Sildenafil vs. Placebo: Hour 24 |
|-----------------------------------|------------------------------------|

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database

(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

| | |
|---|-------------------------|
| Comparison groups | IV Sildenafil v Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1576 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 79.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -32.5 |
| upper limit | 192.2 |

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; medically important events. Treatment-emergent are events between first infusion of study drug and up to 31 days after end of study drug infusion (up to 45 days) that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAEs and non-SAEs. The safety population included all subjects treated with study treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 31 days after end of study drug infusion (up to 45 days)

| End point values | IV Sildenafil | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: subjects | | | | |
| AEs | 22 | 19 | | |
| SAEs | 7 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treatment-Emergent Adverse Events (AEs) According to Severity

| | |
|-----------------|---|
| End point title | Number of Treatment-Emergent Adverse Events (AEs) According to Severity |
|-----------------|---|

End point description:

AE: untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE: AE resulting in any of the following outcomes: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; medically important events. Treatment-emergent are events between first infusion of study drug and up to 31 days after end of study drug infusion (up to 45 days) that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAEs and non-SAEs. Severity criteria: mild=did not interfere with subject's usual function; moderate=interfered to some extent with subject's usual function and severe=interfered significantly with subject's usual function. Missing baseline severities were imputed as mild. The safety population included all subjects treated with study treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 31 days after end of study drug infusion (up to 45 days)

| End point values | IV Sildenafil | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: events | | | | |
| Mild | 49 | 42 | | |
| Moderate | 29 | 24 | | |
| Severe | 12 | 17 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Abnormalities

| | |
|---|--|
| End point title | Number of Subjects With Laboratory Abnormalities |
| End point description: Criteria for laboratory values: Hematology: hemoglobin, hematocrit, red blood cell count <0.8*lower limit of normal (LLN), platelets<0.5*LLN, >1.75*upper limit of normal (ULN), white blood cells count <0.6*LLN, >1.5*ULN; Liver function: total and direct bilirubin >1.5*ULN, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase >3.0*ULN, total protein <0.8*LLN, >1.2*ULN; Renal function: blood urea nitrogen, creatinine >1.3*ULN; Electrolytes: sodium <0.95*LLN, >1.05*ULN, potassium, chloride, calcium, bicarbonate (venous) <0.9*LLN, >1.1*ULN. Here, "number of subjects analyzed" signifies those subjects who were evaluable for this endpoint. The safety population included all subjects treated with study treatment. | |
| End point type | Secondary |
| End point timeframe: Up to 14 days from initiation of study drug infusion | |

| End point values | IV Sildenafil | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: subjects | 27 | 22 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Composite Scores of Cognitive, Language, and Motor Developmental Progress of Subjects as Assessed by Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III)

| | |
|---|---|
| End point title | Part B: Composite Scores of Cognitive, Language, and Motor Developmental Progress of Subjects as Assessed by Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III) |
| End point description: Bayley-III assesses infant and toddler development across five domains: cognitive, language, motor, social-emotional (SE), and adaptive behavior (AB). Assessments of the cognitive, language, and motor domains conducted using items administered to the child; assessments of the SE and AB domains conducted using the primary caregiver's responses to a questionnaire. Score ranges: cognitive scale 0-91, language scale 0-97 and motor scale 0-132, where higher scores indicated better cognitive function, communication and motor skills respectively. Raw scores of cognitive, language and motor domains were converted to composite scores. Composite scores of cognitive, language and motor developmental scales ranged from a scale of 40 to 160, where higher score indicated stronger skills and abilities. Part-B safety analysis set. Number Analysed =subjects evaluable for this end point, n =subjects evaluable for each specified rows. | |
| End point type | Secondary |
| End point timeframe: Month 12 and 24 after end of study treatment in Part A (Day 1 to 14) | |

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 13 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cognitive Development: Month 12 (n =19, 12) | 97.5 (± 16.14) | 94.5 (± 14.18) | | |
| Cognitive Development: Month 24 (n =17, 13) | 97.4 (± 18.12) | 97.3 (± 14.95) | | |
| Language Development: Month 12 (n =18, 12) | 99.5 (± 16.86) | 94.7 (± 10.25) | | |
| Language Development: Month 24 (n =16, 11) | 96.7 (± 21.91) | 95.8 (± 17.70) | | |
| Motor Development: Month 12 (n =19, 12) | 93.1 (± 16.10) | 88.2 (± 14.61) | | |
| Motor Development: Month 24 (n =17, 12) | 99.0 (± 19.59) | 105.3 (± 24.00) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Composite Scores of Social-Emotional and Adaptive Behavior Questionnaire of Subjects as Assessed by Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III)

| | |
|-----------------|--|
| End point title | Part B: Composite Scores of Social-Emotional and Adaptive Behavior Questionnaire of Subjects as Assessed by Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III) |
|-----------------|--|

End point description:

The Bayley-III assesses infant and toddler development across five domains: cognitive, language, motor, social-emotional (SE), and adaptive behavior (AB). Assessments of the cognitive, language, and motor domains conducted using items administered to the child; assessments of the SE and AB domains conducted using the primary caregiver's responses to a questionnaire. The questionnaire comprises the SE scale (35 items) and the AB scale (241 items). Raw scores of SE and AB were converted to composite scores. Composite scores for SE and AB scale ranged from 40 to 160, where higher scores indicated better social-emotional skills and adaptive behavior in child. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. 'Number Analysed' = subjects evaluable for this end point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 8 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Social-Emotional Development | 104.5 (± 21.40) | 112.5 (± 18.13) | | |
| Adaptive Behavior Development | 91.6 (± 15.66) | 98.3 (± 12.44) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects With Eye Movement Disorders as Assessed by Eye Examination

| | |
|-----------------|---|
| End point title | Part B: Number of Subjects With Eye Movement Disorders as Assessed by Eye Examination |
|-----------------|---|

End point description:

Standard age-appropriate ophthalmological examinations of subjects were used to assess eye movement disorders (presence of amblyopia, strabismus, and nystagmus) at month 12 and 24. In this end point, data have been reported for right and left eye separately. Rows according to eye movement disorder categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 14 | | |
| Units: subjects | | | | |
| Strabismus Present,Right Eye: Month 12 (n =16, 14) | 0 | 1 | | |
| Strabismus Present,Left Eye: Month 12 (n =16, 14) | 0 | 1 | | |
| Strabismus Present,Right Eye: Month 24 (n =12, 12) | 1 | 0 | | |
| Strabismus Present,Left Eye: Month 24 (n =12, 12) | 1 | 0 | | |
| Nystagmus Present,Left Eye: Month 24 (n =12, 12) | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Visual Acuity of Verbal Subjects as Assessed by Ophthalmological Assessment

| | |
|-----------------|---|
| End point title | Part B: Visual Acuity of Verbal Subjects as Assessed by Ophthalmological Assessment |
|-----------------|---|

End point description:

Standard age-appropriate ophthalmological examinations were used to assess visual acuity (performed differently for children able of verbal interaction) through visual acuity chart (VAC) quantitative, counting finger (CF), hand motion (HM), light perception (LP), no light perception (NLP) and missing at month 12 and 24. In this end point, data have been reported for right and left eye separately. Rows according to visual acuity categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 14 | | |
| Units: subjects | | | | |
| VAC Quantitative, Right Eye: Month 12 (n =16, 14) | 2 | 1 | | |
| HM, Right Eye: Month 12 (n =16, 14) | 0 | 2 | | |
| LP, Right Eye: Month 12 (n =16, 14) | 1 | 0 | | |
| Missing, Right Eye: Month 12 (n =16, 14) | 13 | 11 | | |
| VAC Quantitative, Left Eye: Month 12 (n =16, 14) | 2 | 1 | | |
| HM, Left Eye: Month 12 (n =16, 14) | 0 | 2 | | |
| LP, Left Eye: Month 12 (n =16, 14) | 1 | 0 | | |
| Missing, Left Eye: Month 12 (n =16, 14) | 13 | 11 | | |
| VAC Quantitative, Right Eye: Month 24 (n =12, 12) | 6 | 5 | | |
| HM, Right Eye: Month 24 (n =12, 12) | 1 | 0 | | |
| Missing, Right Eye: Month 24 (n =12, 12) | 5 | 7 | | |
| VAC Quantitative, Left Eye: Month 24 (n =12, 12) | 6 | 5 | | |

| | | | | |
|---|---|---|--|--|
| Missing, Left Eye: Month 24 (n =12, 12) | 6 | 7 | | |
|---|---|---|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Visual Acuity of Non-Verbal Subjects as Assessed by Ophthalmological Assessment

| | |
|---|---|
| End point title | Part B: Visual Acuity of Non-Verbal Subjects as Assessed by Ophthalmological Assessment |
| End point description: | |
| Standard age-appropriate ophthalmological examinations were used to assess visual acuity (performed differently for children unable of verbal interaction) through fixates and follows [F&F] (included central, steady and maintained), light perception [LP] (wince to light), no light perception [NLP], and missing at month 12 and 24. In this end point, data have been reported for right and left eye separately. Rows according to visual acuity categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows. | |
| End point type | Secondary |
| End point timeframe: | |
| Month 12 and 24 after end of study treatment in Part A (Day 1 to 14) | |

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 14 | | |
| Units: subjects | | | | |
| F&F, Right Eye: Month 12 (n =16, 14) | 15 | 13 | | |
| LP, Right Eye: Month 12 (n =16, 14) | 0 | 1 | | |
| Missing, Right Eye: Month 12 (n =16, 14) | 1 | 0 | | |
| F&F, Left Eye: Month 12 (n =16, 14) | 15 | 13 | | |
| LP, Left Eye: Month 12 (n =16, 14) | 0 | 1 | | |
| Missing, Left Eye: Month 12 (n =16, 14) | 1 | 0 | | |
| F&F, Right Eye: Month 24 (n =12, 12) | 5 | 9 | | |
| Missing, Right Eye: Month 24 (n =12, 12) | 7 | 3 | | |
| F&F, Left Eye: Month 24 (n =12, 12) | 5 | 9 | | |
| Missing, Left Eye: Month 24 (n =12, 12) | 7 | 3 | | |

Statistical analyses

Secondary: Part B: Visual Acuity of Verbal Subjects as Assessed by LogMAR Through Visual Acuity Chart

| | |
|-----------------|--|
| End point title | Part B: Visual Acuity of Verbal Subjects as Assessed by LogMAR Through Visual Acuity Chart |
|-----------------|--|

End point description:

Standard age-appropriate ophthalmological examinations were used to assess visual acuity (performed differently for children able of verbal interaction) at month 12 and 24. Visual acuity (VA) of verbal children was assessed for each eye using the Snellen method, where logarithm of minimum angle of resolution (logMAR) units were derived from the Snellen ratios. Subjects had to read letters from the chart at a distance of 20 feet/6 meter or 4 meter. VA (Snellen ratio) = distance between the chart and subject, divided by distance at which subject was able to see/read chart without impairment; expressed as decimal, logMAR = \log_{10} (1/decimal VA). In this end point, data have been reported for right and left eye separately. Part B safety analysis. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: LogMAR | | | | |
| arithmetic mean (standard deviation) | | | | |
| Right Eye: Month 12 (n =6, 3) | 0.45 (± 0.394) | 0.57 (± 0.513) | | |
| Left Eye: Month 12 (n =6, 3) | 0.47 (± 0.372) | 0.57 (± 0.513) | | |
| Right Eye: Month 24 (n =6, 4) | 0.20 (± 0.155) | 0.28 (± 0.299) | | |
| Left Eye: Month 24 (n =6, 6) | 0.20 (± 0.155) | 0.35 (± 0.409) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Visual Status of Subjects With Abnormality as Assessed by Eye Examination of the Anterior and Posterior Segments

| | |
|-----------------|--|
| End point title | Part B: Visual Status of Subjects With Abnormality as Assessed by Eye Examination of the Anterior and Posterior Segments |
|-----------------|--|

End point description:

Standard age-appropriate ophthalmological examinations were used to assess examination of anterior and posterior chamber for abnormality in lids, conjunctiva, cornea, anterior chamber, lens, iris, pupil, extraocular muscle movement (EMM) and eye movements at month 12 and 24. In this end point, data have been reported for right and left eye separately. Rows according to visual status categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 17 | 15 | | |
| Units: subjects | | | | |
| Anterior (Lids), Right Eye: Month 12 (n =17, 15) | 0 | 1 | | |
| Anterior (Lids), Left Eye: Month 12 (n =17, 15) | 0 | 1 | | |
| Anterior (EMM), Right Eye: Month 24 (n =13, 11) | 1 | 0 | | |
| Anterior (EMM), Left Eye: Month 24 (n =13, 11) | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Behavior Hearing Assessment Through Pure Tone Audiometry Test

| | |
|-----------------|--|
| End point title | Part B: Audiological Status of Subjects as Assessed by Behavior Hearing Assessment Through Pure Tone Audiometry Test |
|-----------------|--|

End point description:

Audiological evaluations of subjects were recorded and reported using behavior hearing assessment through pure tone audiometry test which included subjects with normal, abnormal, incomplete/inconclusive behavior at month 12 and 24. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 12 | | |
| Units: subjects | | | | |
| Normal Behavior: Month12 | 11 | 8 | | |
| Abnormal Behavior: Month 12 | 1 | 4 | | |
| Incomplete/Inconclusive Behavior: Month 12 | 4 | 0 | | |

| | | | | |
|--|----|---|--|--|
| Normal Behavior: Month 24 | 13 | 8 | | |
| Abnormal Behavior: Month 24 | 0 | 2 | | |
| Incomplete/Inconclusive Behavior: Month 24 | 3 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Bone Conduction Through Pure Tone Audiometry Test

| | |
|-----------------|--|
| End point title | Part B: Audiological Status of Subjects as Assessed by Bone Conduction Through Pure Tone Audiometry Test |
|-----------------|--|

End point description:

Audiological evaluations of subjects were recorded and reported by bone conduction assessment through pure tone audiometry test which included subjects with sensorineural hearing loss, conductive hearing loss, mixed hearing loss, neural, and unspecified. Rows according to bone conduction categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1 | 2 | | |
| Units: subjects | | | | |
| Conductive Hearing Loss: Month 12 (n =1, 2) | 0 | 1 | | |
| Unspecified: Month 12 (n =1, 2) | 1 | 1 | | |
| Conductive Hearing Loss: Month 24 (n =0, 1) | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Air Conduction via Phones/Headphones Through Pure Tone Audiometry Test

| | |
|-----------------|---|
| End point title | Part B: Audiological Status of Subjects as Assessed by Air Conduction via Phones/Headphones Through Pure Tone Audiometry Test |
|-----------------|---|

End point description:

Audiological evaluations of subjects were recorded and reported by air conduction via phones/headphones through pure tone audiometry test which included subjects with hearing loss ranged from less than or equal to (\leq) 20 decibel hearing loss (DB HL), 21-40 DB HL, 41-70 DB HL, 71-90 DB HL, greater than ($>$) 90 DB HL or no response, and missing at frequencies ranged from 500 Hertz (Hz) to 8000 Hz at month 12 and 24. In this end point, data have been reported for right and left ear separately. Rows according to air conduction categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. 'Number of Subjects Analysed' = subjects evaluable for this end point and 'n' = number of subjects evaluable for each specified rows.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 8 | 5 | | |
| Units: subjects | | | | |
| Right Ear,500 Hz,<=20 DB HL: Month 12 (n =5, 5) | 3 | 4 | | |
| Right Ear,500 Hz, 21-40 DB HL: Month 12 (n =5, 5) | 2 | 1 | | |
| Right Ear,1000 Hz,<=20 DB HL: Month 12 (n =5, 5) | 4 | 5 | | |
| Right Ear,1000 Hz,21-40 DB HL: Month 12 (n =5, 5) | 1 | 0 | | |
| Right Ear,2000 Hz,<=20 DB HL: Month 12 (n =5, 5) | 3 | 4 | | |
| Right Ear,2000 Hz,21-40 DB HL: Month 12 (n =5, 5) | 2 | 0 | | |
| Right Ear,4000 Hz,<=20 DB HL: Month 12 (n =5, 5) | 4 | 5 | | |
| Right Ear,4000 Hz,21-40 DB HL: Month 12 (n =5, 5) | 1 | 0 | | |
| Right Ear,8000 Hz,<=20 DB HL: Month 12 (n =5, 5) | 3 | 4 | | |
| Right Ear,8000 Hz, Missing: Month 12 (n =5, 5) | 2 | 0 | | |
| Left Ear,500 Hz, <=20 DB HL: Month 12 (n =5, 5) | 3 | 3 | | |
| Left Ear,500 Hz, 21-40 DB HL: Month 12 (n =5, 5) | 2 | 1 | | |
| Left Ear,1000 Hz, <=20 DB HL: Month 12 (n =5, 5) | 3 | 5 | | |
| Left Ear,1000 Hz, 21-40 DB HL: Month 12 (n =5, 5) | 2 | 0 | | |
| Left Ear,2000 Hz, <=20 DB HL: Month 12 (n =5, 5) | 3 | 4 | | |
| Left Ear,2000 Hz, 21-40 DB HL: Month 12 (n =5, 5) | 2 | 0 | | |
| Left Ear,4000 Hz, <=20 DB HL: Month 12 (n =5, 5) | 4 | 5 | | |
| Left Ear,4000 Hz, 21-40 DB HL: Month 12 (n =5, 5) | 1 | 0 | | |

| | | | | |
|--|---|---|--|--|
| Left Ear,8000 Hz, <=20 DB HL: Month 12 (n =5, 5) | 3 | 4 | | |
| Left Ear,8000 Hz, Missing: Month 24 (n =5, 5) | 2 | 1 | | |
| Right Ear,500 Hz, <=20 DB HL: Month 24 (n =8, 4) | 5 | 3 | | |
| Right Ear,500 Hz, 21-40 DB HL: Month 24 (n =8, 4) | 2 | 0 | | |
| Right Ear,1000 Hz, <=20 DB HL: Month 24 (n =8, 4) | 5 | 2 | | |
| Right Ear,1000 Hz, 21-40 DB HL: Month 24 (n =8, 4) | 1 | 0 | | |
| Right Ear,2000 Hz, <=20 DB HL: Month 24 (n =8, 4) | 6 | 3 | | |
| Right Ear,2000 Hz, 21-40 DB HL: Month 24 (n =8, 4) | 1 | 0 | | |
| Right Ear,4000 Hz, <=20 DB HL: Month 24 (n =8, 4) | 7 | 3 | | |
| Right Ear,8000 Hz, <=20 DB HL: Month 24 (n =8, 4) | 4 | 3 | | |
| Right Ear,8000 Hz, 21-40 DB HL: Month 24 (n =8, 4) | 1 | 0 | | |
| Right Ear,8000 Hz, Missing: Month 24 (n =8, 4) | 1 | 0 | | |
| Left Ear,500 Hz, <=20 DB HL: Month 24 (n =8, 4) | 6 | 3 | | |
| Left Ear,500 Hz, 21-40 DB HL: Month 24 (n =8, 4) | 1 | 0 | | |
| Left Ear,1000 Hz, <=20 DB HL: Month 24 (n =8, 4) | 4 | 3 | | |
| Left Ear,1000 Hz, 21-40 DB HL: Month 24 (n =8, 4) | 1 | 0 | | |
| Left Ear,2000 Hz, <=20 DB HL: Month 24 (n =8, 4) | 6 | 2 | | |
| Left Ear,2000 Hz, 21-40 DB HL: Month 24 (n =8, 4) | 1 | 0 | | |
| Left Ear,4000 Hz, <=20 DB HL: Month 24 (n =8, 4) | 7 | 4 | | |
| Left Ear,8000 Hz, <=20 DB HL: Month 24 (n =8, 4) | 3 | 3 | | |
| Left Ear,8000 Hz, 21-40 DB HL: Month 24 (n =8, 4) | 1 | 0 | | |
| Left Ear,8000 Hz, Missing: Month 24 (n =8, 4) | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Air Conduction via Soundfield Through Pure Tone Audiometry Test

| | |
|-----------------|--|
| End point title | Part B: Audiological Status of Subjects as Assessed by Air Conduction via Soundfield Through Pure Tone Audiometry Test |
|-----------------|--|

End point description:

Audiological evaluations of subjects were recorded and reported by air conduction via soundfield through pure tone audiometry test which included subjects with hearing loss ranged from <=20 DB HL, 21-40 DB HL, 41-70 DB HL, 71-90 DB HL, >90 DB HL or no response, and missing at frequencies ranged from 500 Hz to 4000 Hz at month 12 and 24. Rows according to air conduction categories at specified time

points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' = number of subjects evaluable for this end point and 'n' = number of subjects evaluable for each specified rows.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Month 12 and 24 after end of study treatment in Part A (Day 1 to 14) | |

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|---|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 9 | | |
| Units: subjects | | | | |
| 500 Hz, <=20 DB HL: Month 12 (n =13, 9) | 6 | 2 | | |
| 500 Hz, 21-40 DB HL: Month 12 (n =13, 9) | 5 | 6 | | |
| 500 Hz, 71-90 DB HL: Month 12 (n =13, 9) | 1 | 0 | | |
| 1000 Hz, <=20 DB HL: Month 12 (n =13, 9) | 9 | 3 | | |
| 1000 Hz, 21-40 DB HL: Month 12 (n =13, 9) | 1 | 5 | | |
| 1000 Hz, 71-90 DB HL: Month 12 (n =13, 9) | 1 | 0 | | |
| 2000 Hz, <=20 DB HL: Month 12 (n =13, 9) | 7 | 2 | | |
| 2000 Hz, 21-40 DB HL: Month 12 (n =13, 9) | 3 | 4 | | |
| 2000 Hz, Missing: Month 12 (n =13, 9) | 1 | 0 | | |
| 4000 Hz, <=20 DB HL: Month 12 (n =13, 9) | 6 | 4 | | |
| 4000 Hz, 21-40 DB HL: Month 12 (n =13, 9) | 4 | 4 | | |
| 4000 Hz, 71-90 DB HL: Month 12 (n =13, 9) | 1 | 0 | | |
| 500 Hz, <=20 DB HL: Month 24 (n =11, 9) | 6 | 2 | | |
| 500 Hz, 21-40 DB HL: Month 24 (n =11, 9) | 2 | 5 | | |
| 1000 Hz, <=20 DB HL: Month 24 (n =11, 9) | 6 | 6 | | |
| 1000 Hz, 21-40 DB HL: Month 24 (n =11, 9) | 4 | 3 | | |
| 2000 Hz, <=20 DB HL: Month 24 (n =11, 9) | 6 | 3 | | |
| 2000 Hz, 21-40 DB HL: Month 24 (n =11, 9) | 2 | 4 | | |
| 4000 Hz, <=20 DB HL: Month 24 (n =11, 9) | 5 | 4 | | |
| 4000 Hz, 21-40 DB HL: Month 24 (n =11, 9) | 4 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Tympanometry Assessment (Peak Pressure) Through Immittance Audiometry Test

| | |
|-----------------|---|
| End point title | Part B: Audiological Status of Subjects as Assessed by Tympanometry Assessment (Peak Pressure) Through Immittance Audiometry Test |
|-----------------|---|

End point description:

Audiological evaluations of subjects were recorded and reported by tympanometry assessment through immittance audiometry test which included subjects with peak pressure (PP) signs (+) and (-) at month 12 and 24. In this end point, data have been reported for right and left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 9 | 8 | | |
| Units: decapascals | | | | |
| arithmetic mean (standard deviation) | | | | |
| PP for Sign (+), Right Ear: Month 12 (n =7, 3) | 51.89 (± 63.024) | 27.33 (± 26.539) | | |
| PP for Sign (+), Left Ear: Month 12 (n =3, 4) | 5.07 (± 4.900) | 73.75 (± 28.987) | | |
| PP for Sign (+), Right Ear: Month 24 (n =3, 4) | 44.00 (± 46.130) | 33.50 (± 44.125) | | |
| PP for Sign (+), Left Ear: Month 24 (n =7, 5) | 42.71 (± 50.112) | 35.00 (± 46.578) | | |
| PP for Sign (-), Right Ear: Month 12 (n =6, 8) | 149.3 (± 144.34) | 67.75 (± 57.350) | | |
| PP for Sign (-), Left Ear: Month 12 (n =9, 5) | 79.89 (± 64.367) | 46.80 (± 46.912) | | |
| PP for Sign (-), Right Ear: Month 24 (n =8, 3) | 98.00 (± 55.685) | 83.67 (± 107.38) | | |
| PP for Sign (-), Left Ear: Month 24 (n =6, 2) | 102.2 (± 84.781) | 135.0 (± 70.711) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Tympanometry Assessment (Static Acoustic Admittance) Through Immittance Audiometry Test

| | |
|-----------------|--|
| End point title | Part B: Audiological Status of Subjects as Assessed by Tympanometry Assessment (Static Acoustic Admittance) Through Immittance Audiometry Test |
|-----------------|--|

End point description:

Audiological evaluations of subjects were recorded and reported by tympanometry assessment through immittance audiometry test which included subjects with static acoustic admittance at month 12 and 24. In this end point, data have been reported for right and left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 9 | 11 | | |
| Units: millimho | | | | |
| arithmetic mean (standard deviation) | | | | |
| Right Ear: Month 12 (n =9, 11) | 0.241 (± 0.1403) | 0.403 (± 0.1691) | | |
| Left Ear: Month 12 (n =8, 9) | 0.364 (± 0.1513) | 0.330 (± 0.1595) | | |
| Right Ear: Month 24 (n =6, 6) | 0.273 (± 0.0784) | 0.400 (± 0.1321) | | |
| Left Ear: Month 24 (n =8, 6) | 0.295 (± 0.0691) | 0.585 (± 0.5558) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Ipsilateral Stapedial Reflex Through Immittance Audiometry Test

| | |
|-----------------|--|
| End point title | Part B: Audiological Status of Subjects as Assessed by Ipsilateral Stapedial Reflex Through Immittance Audiometry Test |
|-----------------|--|

End point description:

Audiological evaluations of subjects were recorded and reported by ipsilateral stapedial reflex through immittance audiometry test which included subjects with presence of ipsilateral stapedial reflex at frequencies ranged from 500 Hz to 2000 Hz at month 12 and 24. Ipsilateral stapedial reflex measures are used to assess the neural pathway surrounding the stapedial reflex, which occurs in response to a loud sound (70 to 90 decibel above threshold). In this end point, data have been reported for right and

left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Month 12 and 24 after end of study treatment in Part A (Day 1 to 14) | |

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 12 | | |
| Units: subjects | | | | |
| 500 Hz, Right Ear: Month 12 (n =14, 12) | 5 | 1 | | |
| 500 Hz, Left Ear: Month 12 (n =14, 12) | 6 | 1 | | |
| 1000 Hz, Right Ear: Month 12 (n =14, 12) | 5 | 1 | | |
| 1000 Hz, Left Ear: Month 12 (n =14, 12) | 6 | 1 | | |
| 2000 Hz, Right Ear: Month 12 (n =14, 12) | 5 | 1 | | |
| 2000 Hz, Left Ear: Month 12 (n =14, 12) | 6 | 1 | | |
| 500 Hz, Right Ear: Month 24 (n =13, 9) | 4 | 2 | | |
| 500 Hz, Left Ear: Month 24 (n =13, 9) | 4 | 2 | | |
| 1000 Hz, Right Ear: Month 24 (n =13, 9) | 4 | 2 | | |
| 1000 Hz, Left Ear: Month 24 (n =13, 9) | 5 | 2 | | |
| 2000 Hz, Right Ear: Month 24 (n =13, 9) | 4 | 2 | | |
| 2000 Hz, Left Ear: Month 24 (n =13, 9) | 4 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Transient Evoked Emission Through Otoacoustic Emissions Assessment

| | |
|-----------------|---|
| End point title | Part B: Audiological Status of Subjects as Assessed by Transient Evoked Emission Through Otoacoustic Emissions Assessment |
|-----------------|---|

End point description:

Audiological evaluations of subjects were recorded and reported by transient evoked emission through otoacoustic emissions assessment which included subjects with presence of transient evoked emissions at frequencies ranged from 1000 Hz to 4000 Hz at month 12 and 24. In this end point, data have been reported for right and left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 7 | 3 | | |
| Units: subjects | | | | |
| 1000 Hz, Right Ear: Month 12 | 3 | 2 | | |
| 1000 Hz, Left Ear: Month 12 | 2 | 1 | | |
| 1500 Hz, Right Ear: Month 12 | 3 | 2 | | |
| 1500 Hz, Left Ear: Month 12 | 2 | 2 | | |
| 2000 Hz, Right Ear: Month 12 | 5 | 2 | | |
| 2000 Hz, Left Ear: Month 12 | 5 | 2 | | |
| 3000 Hz, Right Ear: Month 12 | 4 | 2 | | |
| 3000 Hz, Left Ear: Month 12 | 4 | 2 | | |
| 4000 Hz, Right Ear: Month 12 | 6 | 2 | | |
| 4000 Hz, Left Ear: Month 12 | 5 | 3 | | |
| 1000 Hz, Right Ear: Month 24 | 3 | 2 | | |
| 1000 Hz, Left Ear: Month 24 | 2 | 2 | | |
| 1500 Hz, Right Ear: Month 24 | 2 | 3 | | |
| 1500 Hz, Left Ear: Month 24 | 2 | 3 | | |
| 2000 Hz, Right Ear: Month 24 | 7 | 3 | | |
| 2000 Hz, Left Ear: Month 24 | 6 | 3 | | |
| 3000 Hz, Right Ear: Month 24 | 6 | 3 | | |
| 3000 Hz, Left Ear: Month 24 | 4 | 3 | | |
| 4000 Hz, Right Ear: Month 24 | 7 | 3 | | |
| 4000 Hz, Left Ear: Month 24 | 5 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Distort Product Through Otoacoustic Emissions Assessment

| | |
|-----------------|---|
| End point title | Part B: Audiological Status of Subjects as Assessed by Distort Product Through Otoacoustic Emissions Assessment |
|-----------------|---|

End point description:

Audiological evaluations of subjects were recorded and reported by distort product through otoacoustic emissions assessment which included subjects with presence of distort product at frequencies ranged from 2000 Hz to 8000 Hz at month 12 and 24. Distortion-product otoacoustic emissions (DPOAEs) are generated in the cochlea in response to two tones of a given frequency and sound pressure level presented in the ear canal. Distort product otoacoustic emissions are an objective indicator of normally functioning cochlea outer hair cells. In this end point, data have been reported for right and left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Month 12 and 24 after end of study treatment in Part A (Day 1 to 14) | |

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 7 | 7 | | |
| Units: subjects | | | | |
| 2000 Hz, Right Ear: Month 12 (n =6, 6) | 4 | 4 | | |
| 2000 Hz, Left Ear: Month 12 (n =6, 6) | 5 | 3 | | |
| 3000 Hz, Right Ear: Month 12 (n =6, 6) | 5 | 4 | | |
| 3000 Hz, Left Ear: Month 12 (n =6, 6) | 5 | 3 | | |
| 4000 Hz, Right Ear: Month 12 (n =6, 6) | 5 | 4 | | |
| 4000 Hz, Left Ear: Month 12 (n =6, 6) | 5 | 3 | | |
| 6000 Hz, Right Ear: Month 12 (n =6, 6) | 4 | 4 | | |
| 6000 Hz, Left Ear: Month 12 (n =6, 6) | 5 | 4 | | |
| 8000 Hz, Right Ear: Month 12 (n =6, 6) | 4 | 2 | | |
| 8000 Hz, Left Ear: Month 12 (n =6, 6) | 5 | 2 | | |
| 2000 Hz, Right Ear: Month 24 (n =7, 7) | 4 | 7 | | |
| 2000 Hz, Left Ear: Month 24 (n =7, 7) | 4 | 6 | | |
| 3000 Hz, Right Ear: Month 24 (n =7, 7) | 7 | 5 | | |
| 3000 Hz, Left Ear: Month 24 (n =7, 7) | 6 | 5 | | |
| 4000 Hz, Right Ear: Month 24 (n =7, 7) | 6 | 5 | | |
| 4000 Hz, Left Ear: Month 24 (n =7, 7) | 6 | 5 | | |
| 6000 Hz, Right Ear: Month 24 (n =7, 7) | 4 | 6 | | |
| 6000 Hz, Left Ear: Month 24 (n =7, 7) | 5 | 6 | | |
| 8000 Hz, Right Ear: Month 24 (n =7, 7) | 3 | 2 | | |
| 8000 Hz, Left Ear: Month 24 (n =7, 7) | 4 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs), and Deaths

| | |
|--|---|
| End point title | Part B: Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs), and Deaths |
| End point description: | |
| An AE was any untoward medical occurrence in a subject who received study medication without regard to possibility of causal relationship to it. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/ incapacity; congenital anomaly. AEs included both serious and all non-serious AEs. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. | |
| End point type | Secondary |

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 26 | | |
| Units: subjects | | | | |
| AEs | 17 | 17 | | |
| SAEs | 9 | 6 | | |
| Deaths | 0 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Neurological Progress of Subjects as Assessed by the Neurology Optimality Score

| | |
|-----------------|---|
| End point title | Part B: Neurological Progress of Subjects as Assessed by the Neurology Optimality Score |
|-----------------|---|

End point description:

The Hammersmith Infant Neurological Examination (HINE) was a standard scoring examination to assess development of cranial nerve; posture; movement; tone; and reflexes and reaction. HINE exam global score is a sum of subset (cranial nerve, posture, movement, tone, reflexes and reactions) scores, ranged from 0 to 78, where higher score represents better outcome. Here, the HINE global scores were reported at month 12 and 24. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and 'n' signifies number of subjects evaluable for each specified rows.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

| End point values | Part B (Non-Interventional Phase): IV Sildenafil | Part B (Non-Interventional Phase): Placebo | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 12 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 12 (n =21, 12) | 69.9 (± 14.97) | 75.6 (± 3.45) | | |
| Month 24 (n =17, 10) | 65.6 (± 19.71) | 76.5 (± 2.42) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part A: Baseline up to 31 days after end of study drug infusion (up to 45 days); Part B: up to 24 months after end of study treatment in Part A (maximum up to 26 months)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event. Deaths (all causes) included only treatment emergent serious events. For Part-B (non-interventional) only SAEs and death data was collected.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Part A: IV Sildenafil |
|-----------------------|-----------------------|

Reporting group description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|-----------------------|-----------------|
| Reporting group title | Part A: Placebo |
|-----------------------|-----------------|

Reporting group description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

| | |
|-----------------------|-----------------------|
| Reporting group title | Part B: IV Sildenafil |
|-----------------------|-----------------------|

Reporting group description:

Subjects who started Part A (not necessarily completed Part A) and who were eligible and consented, continued to be followed up in part B of the study.

| | |
|-----------------------|-----------------|
| Reporting group title | Part B: Placebo |
|-----------------------|-----------------|

Reporting group description:

Subjects who started Part A (not necessarily completed Part A) and who were eligible and consented, continued to be followed up in part B of the study.

| Serious adverse events | Part A: IV Sildenafil | Part A: Placebo | Part B: IV Sildenafil |
|---|-----------------------|-----------------|-----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 2 / 30 (6.67%) | 9 / 27 (33.33%) |
| number of deaths (all causes) | 1 | 1 | 0 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|----------------|----------------|----------------|
| complications | | | |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Pulmonary malformation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Congenital heart disease | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Myoclonus | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Drug withdrawal syndrome | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Food allergy | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal Reflux | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Apnoea | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension crisis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 2 / 27 (7.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 2 / 27 (7.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|--|--|
| Serious adverse events | Part B: Placebo | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Pulmonary malformation | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital heart disease | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Myoclonus | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| General disorders and administration site conditions | | | |
| Drug withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Food allergy | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroesophageal Reflux | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary hypertension crisis | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung disorder | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Part A: IV Sildenafil | Part A: Placebo | Part B: IV Sildenafil |
|---|-----------------------|------------------|-----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 29 (68.97%) | 19 / 30 (63.33%) | 0 / 27 (0.00%) |
| Vascular disorders | | | |
| Haemodynamic instability | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 3 / 30 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 7 | 3 | 0 |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Drug withdrawal syndrome | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Drug withdrawal syndrome neonatal | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Generalised oedema | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oedema | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 3 / 30 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Secretion discharge | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Reproductive system and breast disorders | | | |
| Oedema genital | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 30 (6.67%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Choking | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hiccups | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lung disorder | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Neonatal asphyxia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 4 / 30 (13.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pulmonary air leakage | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pulmonary interstitial emphysema syndrome | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 30 (6.67%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Respiratory tract oedema | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stridor | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|--|---------------------|----------------------|---------------------|
| Tachypnoea subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Psychiatric disorders Selective eating disorder subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Blood calcium decreased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Blood magnesium decreased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Blood methaemoglobin present subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 2 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Blood urea increased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 3 / 30 (10.00%) 4 | 0 / 27 (0.00%) 0 |
| Haematocrit decreased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Hepatic enzyme increased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Oxygen saturation decreased | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| PCO2 decreased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Staphylococcus test positive subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Thyroid function test abnormal subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural hypertension subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Procedural hypotension subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Transfusion reaction subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Underdose subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Congenital, familial and genetic disorders | | | |
| Persistent foetal circulation subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Bradycardia neonatal | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Junctional ectopic tachycardia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |
| Brain injury | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypertonia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Motor dysfunction | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Seizure | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 4 / 29 (13.79%) 5 | 3 / 30 (10.00%) 3 | 0 / 27 (0.00%) 0 |
| Leukocytosis subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Eye disorders | | | |
| Eye oedema subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Periorbital oedema subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Pupil fixed subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Gastric haemorrhage subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 2 | 0 / 27 (0.00%) 0 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Intestinal perforation subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Vomiting | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | 0 / 27 (0.00%) 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 3 / 30 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 30 (6.67%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin irritation | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Oliguria | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nosocomial infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 30 (6.67%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alkalosis hypochloraemic | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Feeding intolerance | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fluid overload | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Fluid retention | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hyperchloraemia | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypochloraemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|-----------------|--|--|
| Non-serious adverse events | Part B: Placebo | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| Vascular disorders | | | |
| Haemodynamic instability | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Drug withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Drug withdrawal syndrome neonatal | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infusion site extravasation | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Secretion discharge | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Withdrawal syndrome | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 | | |
| Reproductive system and breast disorders Oedema genital subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders Atelectasis subjects affected / exposed occurrences (all) Choking subjects affected / exposed occurrences (all) Hiccups subjects affected / exposed occurrences (all) Hypoxia subjects affected / exposed occurrences (all) Lung disorder subjects affected / exposed occurrences (all) Neonatal asphyxia subjects affected / exposed occurrences (all) Pneumothorax subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all) Pulmonary air leakage subjects affected / exposed occurrences (all) Pulmonary interstitial emphysema syndrome | 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 | | |

| | | | |
|------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory tract oedema | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stridor | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Selective eating disorder | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood calcium decreased | | | |

| | | | |
|----------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood methaemoglobin present | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haematocrit decreased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| PCO2 decreased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Staphylococcus test positive | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thyroid function test abnormal | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural | | | |

| | | | |
|--|----------------|--|--|
| complications | | | |
| Procedural hypertension | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Procedural hypotension | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Underdose | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Congenital, familial and genetic disorders | | | |
| Persistent foetal circulation | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bradycardia neonatal | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Junctional ectopic tachycardia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|---------------------|--|--|
| Nervous system disorders Brain injury subjects affected / exposed occurrences (all) Cerebral ischaemia subjects affected / exposed occurrences (all) Hypertonia subjects affected / exposed occurrences (all) Motor dysfunction subjects affected / exposed occurrences (all) Seizure subjects affected / exposed occurrences (all) Vocal cord paralysis subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |
| Eye disorders Eye oedema subjects affected / exposed occurrences (all) Periorbital oedema subjects affected / exposed occurrences (all) Pupil fixed | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |
| | 0 / 26 (0.00%) 0 | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin irritation | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Oliguria | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nosocomial infection | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tracheitis | | | |

| | | | |
|------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alkalosis hypochloraemic | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Feeding intolerance | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperchloraemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypochloraemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported